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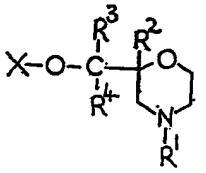
(54) ARYLOXYALKYLMORPHOLINE DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new morpholine derivatives which possess valuable therapeutic properties, for example they possess depressant action on the central nervous system of warm-blooded animals as demonstrated by the reduction of spontaneous motility of mice, a standard test for central nervous depressant activity, and they are therefore useful in the treatment of anxiety and neurotic states in man. Furthermore, the compounds also possess thymoleptic activity in warm-blooded animals as demonstrated by the reversal of reserpine-induced hypothermia in mice, a standard test for thymoleptic activity, and these compounds are therefore useful in the treatment of prophylaxis of depressive illness in man.

According to the invention there are provided new morpholine derivatives of the formula:—



wherein R^1 stands for hydrogen or for an alkyl, alkenyl or cycloalkyl radical, wherein R^2, R^3 and R^4, which may be the same or different, stand for hydrogen or for alkyl radicals, provided that R^2, R^3 and R^4 do not all stand for hydrogen, or wherein R^2 and R^3 are joined, together with the two adjacent carbon atoms, to form a cycloalkyl ring and R^4 stands for hydrogen or for an alkyl radical, and wherein X stands for an aryl radical which may optionally be substituted, and the acid-addition salts thereof.

It is to be understood that the above definition of morpholine derivatives encompass all possible stereoisomers thereof, and mixtures thereof, and in particular it includes individual optically-active enantiomorphs and racemic mixtures.

A suitable value for R^1 when it stands for an alkyl radical is, for example, an alkyl radical of up to 6 carbon atoms, for example the methyl, ethyl, isopropyl, n-propyl, s-butyl or t-butyl radical.

A suitable value for R^1 when it stands for an alkenyl radical is, for example, an alkenyl radical of up to 6 carbon atoms, for example the allyl radical.

A suitable value for R^1 when it stands for a cycloalkyl radical is, for example, a cycloalkyl radical of up to 5 carbon atoms, for example the cyclopropyl, cyclobutyl or cyclopentyl radical.

A suitable value for R^2, R^3 and R^4 when it stands for an alkyl radical is, for example, an alkyl radical of up to 3 carbon atoms, for example the methyl, ethyl or n-propyl radical.

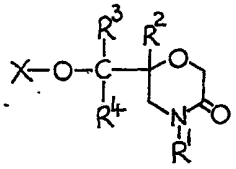
A suitable value for the cycloalkyl ring formed by R^2, R^3 and the two adjacent carbon atoms is, for example, a cycloalkyl ring of up to 8 carbon atoms, for example the cyclohexyl ring.

A suitable value for X is, for example, a phenyl or naphthyl radical which is unsubstituted or which is substituted by one or more substituents, and particularly one or two substituents, selected from halogen atoms, for example fluorine, chlorine, bromine and iodine atoms; alkyl, alkoxy and alkylthio radicals, for example alkyl, alkoxy and alkylthio radicals each of up to 10 carbon atoms, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, t-amyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, n-heptyloxy and methylthio radicals; halogenoalkyl and halogenoalkoxy radicals, for example halogenoalkyl and halogenoalkoxy radicals each of up to 5 carbon atoms, for example trifluoromethyl and 2,2 - dichloro - 1,1 - difluoroethoxy radicals; alkenyl, alkenyloxy, alkynyloxy and cycloalkoxy radicals, for example alkenyl, alkenyloxy, alkynyloxy and cycloalkoxy radicals each of up to 6 carbon atoms, for example allyl, allyloxy, propargyloxy and cyclopentyloxy radicals; aryl, aryloxy, alkylaryloxy, aralkyl and aralkoxy radicals, for example aryl, aryloxy, alkylaryloxy, aralkyl and aralkoxy radicals each of up to 10 carbon atoms, for example phenyl, phenoxy, 4-tolyloxy, benzyl and benzyloxy radicals; hydroxyalkyl and alkoxyalkyl radicals, for example alkyl radicals of up to 5 carbon atoms substituted by hydroxy radicals or by alkoxy radicals of up to 5 carbon atoms, for example hydroxymethyl, 1-hydroxyethyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl and n-propoxymethyl radicals; acyl radicals, for example alkanoyl radicals of up to 5 carbon atoms, for example acetyl radicals; acylamino radicals, for example alkanoylamino radicals of up to 6 carbon atoms, for example acetamido radicals; alkoxycarbonyl radicals, for example alkoxycarbonyl radicals of up to 6 carbon atoms, for example methoxycarbonyl and ethoxycarbonyl radicals; hydroxy, amino, carboxy, methylenedioxy and nitro radicals; and alkylene radicals, for example alkylene radicals of 3 or 4 carbon atoms, for example trimethylene and tetramethylene radicals (that is, those radicals which, together with the aryl radical X, form an indanyl or tetrahydronaphthyl radicals, for example the 4-indanyl, 5-indanyl, 5,6,7,8-tetrahydro-1-naphthyl or 5,6,7,8-tetrahydro-2-naphthyl radical).

Specific compounds of the invention are, for example, those hereinafter particularly disclosed in Examples 1 to 16, and of these preferred compounds are 2 - (1 - methyl - 1-phenoxyethyl)morpholine; 2 - (1 - phenoxyethyl)morpholine; 2 - methyl - 2 - phenoxymethylmorpholine; 2 - (1 - *o* - ethoxyphenoxy - 1 - methylethyl)morpholine and 2-(1 - *o* - ethoxyphenoxy - 1 - methylethyl) - 4-isopropylmorpholine and the acid-addition salts thereof.

Suitable acid-addition salts of the morpholine derivatives of the invention are, for example, acid-addition salts derived from an inorganic or organic acid, for example hydrochlorides, hydrobromides, phosphates, sulphates, oxalates, lactates, tartrates, acetates, gluconates, salicylates, citrates, ascorbates, benzoates, β-naphthoates, adipates or 1,1-methylene - bis - (2 - hydroxy - 3 - naphthoates) or acid-addition salts derived from acidic synthetic resins, for example sulphonated polystyrene resins, for example "Zeo-Karb" 225 ("Zeo-Karb" is a Trade Mark).

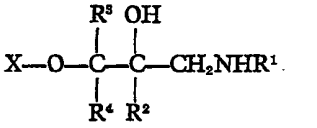
According to a further feature of the invention there is provided a process for the manufacture of the morpholine derivatives of the invention, which comprises the reduction of a compound of the formula:—



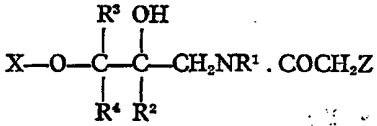
wherein R^1, R^2, R^3, R^4 and X have the meanings stated above, with a complex metal hydride.

The complex metal hydride may be, for example, an alkali metal aluminium hydride, for example lithium aluminium hydride. The reduction may be carried out in an inert diluent or solvent, for example ether, tetrahydrofuran or 1,2-dimethoxyethane, and it may be accelerated or completed by the application of heat, for example by heating to the boiling point of the diluent or solvent.

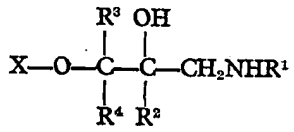
The starting material for the above process may be obtained by the interaction of a compound of the formula:—



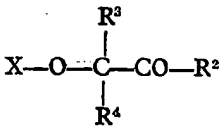
wherein R^1, R^2, R^3, R^4 and X have the meanings stated above, with a compound of the formula $ZCH_2—COZ^1$, wherein Z and Z^1, which may be the safe or different, stand for halogen atoms, for example chlorine or bromine atoms, followed by the cyclisation of the compound of the formula:—



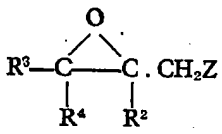
thus obtained. The compound of the formula:—



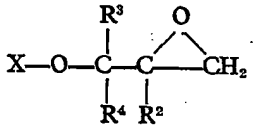
may itself be obtained by the reaction of a carbonyl compound of the formula:—



wherein R^2, R^3, R^4 and X have the meanings stated above, with dimethylsulphoxonium methylide, or by the reaction of a phenol of the formula X—OH, wherein X has the meaning stated above, with an epihalohydrin of the formula:—

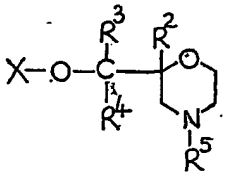


wherein R^2, R^3, R^4 and Z have the meanings stated above, followed by the reaction of the epoxide of the formula:—



wherein R^2, R^3, R^4 and X have the meanings stated above, which is obtained by either of the above reactions, with an amine of the formula R^1NH_2, wherein R^1 has the meaning stated above, as generally described in United Kingdom Patent Specifications Nos. 994,918, 1,023,214 and 1,069,345.

According to a further feature of the invention there is provided a process for the manufacture of those of the morpholine derivatives of the invention wherein R^1 stands for hydrogen which comprises the removal of the removable α-aryl-alkyl or alkyl radical from a compound of the formula:—



wherein R^2, R^3, R^4 and X have the meanings stated above and wherein R^5 stands for a removable α-aryl-alkyl or alkyl radical.

A suitable value for R^5 when it stands for a removable α-aryl-alkyl radical is, for example, an alkyl radical of up to 4 carbon atoms which is substituted on the α-carbon by a phenyl radical, for example the benzyl radicals. A suitable value for R^5 when it stands for a removable alkyl radical is, for example, an alkyl radical of up to 6 carbon atoms, for example the methyl or isopropyl radical.

The α-aryl-alkyl radical may be removed by catalytic hydrogenolysis, for example by means of hydrogen in the presence of a palladium-on-charcoal catalyst, in a diluent or solvent. The catalytic hydrogenolysis is conveniently carried out at ambient temperature and at atmospheric pressure, and is conveniently accelerated by the presence of an acidic catalyst, for example hydrochloric acid.

Alternatively, the α-aryl-alkyl or alkyl radical may be removed by the interaction of the compound of the formula given above with an alkyl or aryl chloroformate, for example methyl, ethyl or phenyl chloroformate, during which interaction the α-aryl-alkyl or alkyl radical is replaced by an alkoxy- or aryloxy-carbonyl radicals, for example the methoxycarbonyl, ethoxycarbonyl or phenoxycarbonyl radical. The said alkoxycarbonyl radical may then be removed by hydrolysis or the alkoxy- or aryloxy-carbonyl derivative obtained as intermediate.

The interaction of the α-aryl-alkyl or alkyl derivative with the alkyl chloroformate may be carried out in a diluent or solvent, for example benzene, and it may be accelerated or completed by the application of heat, for example by heating to the boiling point of the diluent or solvent.

The hydrolysis of the alkoxycarbonyl derivative may be carried out by means of an alkali, for example sodium or potassium hydroxide, and it may be carried out in an aqueous diluent or solvent, for example water, aqueous methanol or aqueous ethanol. The hydrolysis may be accelerated or completed by the application of heat, for example by heating to the boiling point of the diluent or solvent.

It is to be understood that if the aryl radical X contains a reactive substituent, for example an unsaturated substituent, for example an alkenyl, alkenyloxy or alkynyloxy radical, or a hydrogenolysable substituent, for example the benzyloxy radical, or a halogen substituent, for example the chlorine atom, and if the α-aryl-alkyl radical is removed by catalytic hydrogenolysis, then the reactive substituent may itself be modified. Thus, an alkenyl radical may be reduced to an alkyl radical; an alkenyloxy or alkynyloxy radical may be reduced to an alkoxy radical; the benzyloxy radical may be hydrogenolysed to the hydroxy radical; and the chlorine atom may be re-

placed by the hydrogen atom. Accordingly, if a reactive substituent as defined above is present in the aryl radical X, and this substituent is to be maintained, or if an alkylthio substituent which might poison a catalyst is present in the aryl radical X, the alternative procedure using an alkyl or aryl chloroformate is preferred for the removal of the α-arylalkyl radical.

The starting material in the last-mentioned process of the invention may be obtained by the reduction of the corresponding morpholin-5-one derivative with a complex metal hydride, for example lithium aluminium hydride, by a similar process to that described above for the manufacture of the morpholine derivatives of the invention.

The morpholine derivatives of the invention may be converted into acid-addition salts thereof by the reaction of the morpholine derivatives in free base form with an acid by conventional means.

According to a further feature of the invention there are provided pharmaceutical compositions which comprise as active ingredient at least one of the morpholine derivatives of the invention or an acid-addition salt thereof, in association with a pharmaceutically-acceptable diluent or carrier therefore.

The pharmaceutical compositions may be, for example, in a form suitable for oral or parenteral administration, for which purposes they may be formulated by means known to the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, emulsions, injectable aqueous or oily solutions or suspensions, or dipersible powders.

The pharmaceutical compositions of the invention may also contain, in addition to the morpholine derivative or salt thereof, one or more known drugs selected from neuroleptic agents, for example chlorpromazine, prochlorperazine, trifluoperazine and haloperidol; other sedative drugs and tranquillizers, for example chlordiazepoxide, phenobarbitone and amylobarbitone; anticonvulsant drugs, for example primidone and phenytoin; β-adrenergic blocking agents, for example propranolol; drugs used in the treatment of Parkinson's disease, for example benzhexol; and other antidepressant drugs, for example imipramine, desipramine, amitriptyline, nortriptyline, drugs of the amphetamine type and monoamineoxidase inhibitors, for example phenelzine and mebanazine.

Preferred pharmaceutical compositions of the invention are those suitable for oral administration in unit dosage form, for example tablets and capsules, which contain between 1 and 100 mg. of active ingredient.

The pharmaceutical compositions of the invention will normally be administered to man, both for the treatment of anxiety and neurotic states and for the treatment of prophylaxis of depressive illness, at such a dose that each patent receives a total of between 5 and 400 mg. of active ingredient per day, and preferably, if a highly active compound is used, a total of between 5 and 40 mg. per day, the composition being administered 3 or 4 times per day.

The invention is illustrated but not limited by the following Examples:—

Example 1

A solution of 1.1 g. of 4-benzyl-2-methyl-2-phenoxymethyl-morpholine hydrochloride methanolate in 30 ml. of absolute ethanol is shaken with 0.3 g. of a 30% palladium-on-charcoal catalyst in an atmosphere of hydrogen at room temperature and at a pressure of one atmosphere until uptake of hydrogen ceases. The mixture is filtered and the solvent is removed by evaporation under reduced pressure. To the residue are added 50 ml. of aqueous 2N-sodium hydroxide solution and the basic mixture is extracted three times with 30 ml. of ethyl acetate each time. The combined ethyl acetate extracts are washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. The residual free base is converted into the oxalate thereof by conventional means, and the oxalate is crystallised from a mixture of acetone and methanol. There is thus obtained 2 - methyl - 2 - phenoxymethylmorpholine oxalate, m.p. 168—172° C.

The 4 - benzyl - 2 - methyl - 2 - phenoxymethylmorpholine hydrochloride methanolate used as starting material may be obtained as follows:—

4.32 G. of a 50% dispersion of sodium hydride in mineral oil are added to a solution of 19.8 g. of trimethylsulphoxonium iodide in 160 ml. of dry dimethylsulphoxide which is maintained in an atmosphere of dry nitrogen. The mixture is stirred at 50—60° C. for 30 minutes and there is thus obtained a mixture containing dimethylsulphoxonium methylide. To this mixture is added a solution of 12.0 g. of phenoxyacetone in 40 ml. of dry dimethylsulphoxide, and the mixture is stirred and heated at 50—60° C. for three hours and then cooled. 1 Litre of water is added, the aqueous mixture is extracted three times with 250 ml. of ethyl acetate each time and the combined ethyl acetate extracts are washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. There is thus obtained as residue 1,2-epoxy-2-methyl-3-phenoxypropane. A mixture of this product and 12.5 ml. of benzylamine is stirred and heated at 140° C. for 18 hours, cooled and extracted with 500 ml. of petroleum ether (b.p. 60—80° C.). The petroleum ether solution is extracted four times with 200 ml. of aqueous 2N-hydrochloric acid each time, a thick brown oil being precipitated in each acidic extract. The com-

bined oil and aqueous acidic extracts are basified with aqueous 2N-sodium hydroxide solution and the mixture is extracted three times with 200 ml. of ethyl acetate each time. The combined ethyl acetate extracts are washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. The residual free base is converted into the oxalate thereof by conventional means, and the oxalate is crystallised from methanol. There is thus obtained 1-benzylamino - 2 - methyl - 3 - phenoxy-2-propanol oxalate, m.p. 174—177° C.

To a stirred, ice-cooled solution of 8.13 g. of 1 - benzylamino - 2 - methyl - 3 - phenoxy-2-propanol (isolated from the oxalate by conventional means) in 200 ml. of dry methylene chloride are added, dropwise and simultaneously, solutions of 3.39 g. of chloroacetyl chloride in 30 ml. of dry methylene chloride and of 3.03 g. of triethylamine in 30 ml. of dry methylene chloride, at such a rate that the temperature of the mixture remains below 10° C. When addition is complete the mixture is stirred at ambient temperature for 18 hours, washed with aqueous 2N-hydrochloric acid and then with water, dried and evaporated to dryness under reduced pressure. There is thus obtained as residue 1-(*N*-benzyl - chloroacetamido) - 2 - methyl - 3-phenoxy-2-propanol. A solution of this product in 50 ml. of dry methanol is added to a solution of 0.69 g. of sodium in 100 ml. of dry methanol and the mixture is stirred and heated under reflux for 6 hours and then evaporated to dryness under reduced pressure. The residue is partitioned between 100 ml. of water and 100 ml. of ethyl acetate and the aqueous layer is extracted twice with 50 ml. of ethyl acetate each time. The combined ethyl acetate solutions are washed with aqueous 2N-hydrochloric acid and then with water, dried and evaporated to dryness under reduced pressure. The residue is crystallised from a mixture of petroleum ether (b.p. 60—80° C.) and ethyl acetate and there is thus obtained 4 - benzyl - 2 - methyl - 2 - phenoxymethylmorpholin-5-one, m.p. 82—84° C.

A solution of 3.1 g. of 4-benzyl-2-methyl-2-phenoxymethylmorpholin-5-one in 100 ml. of dry ether is added dropwise to a stirred suspension of 1.1 g. of lithium aluminium hydride in 100 ml. of dry ether at such a rate that gentle reflux takes place. When the addition is complete the mixture is stirred and heated under reflux for 4 hours, and is then stirred at room temperature for 18 hours. The mixture is cooled in ice and stirred during successive addition of 1.1 ml. of water, 1.1 ml. of aqueous 2N-sodium hydroxide solution and 3.3 ml. of water. The mixture is filtered and the ethereal solution is dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. The residual free base is converted to the hydrochloride thereof by conventional means and the hydrochloride is crystallised from a mixture of methanol and ether. There is thus obtained 4 - benzyl - 2 - methyl - 2 - phenoxymethylmorpholine hydrochloride containing methanol of crystallisation, m.p. 112—114° C. with decomposition.

Example 2

A solution of 2.1 g. of 4-benzyl-2-(1-methyl-1-phenoxyethyl)-morpholine hydrochloride in a mixture of 40 ml. of absolute ethanol and 40 ml. of water is shaken with 0.5 g. of a 5% palladium-on-charcoal catalyst in an atmosphere of hydrogen at room temperature and at a pressure of one atmosphere until uptake of hydrogen ceases. The mixture is filtered, the filtrate is evaporated to dryness under reduced pressure and the residue is crystallised from a mixture of ethanol and ether. There is thus obtained 2-(1-methyl-1-phenoxyethyl)morpholine hydrochloride, m.p. 129.5—130.5° C.

The 4 - benzyl - 2 - (1 - methyl - 1-phenoxyethyl)morpholine hydrochloride used as starting material may be obtained by a similar process to that described in the second part of Example 1, except that 18.0 g. of 2 - methyl - 2 - phenoxypropionaldehyde are used in place of the 12.0 g. phenoxyacetone, and equivalent amounts of the other reagents and solvents are used. There are thus obtained successively 1,2-epoxy-3-methyl - 3 - phenoxybutane-1-benzyl-amino-3-methyl-3-phenoxy-2-butanol (characterised as the hydrogen oxalate, m.p. 199—201° C. after crystallisation from a mixture of ethanol and ether); 1 - (*N* - benzylchloroacetamido) - 3 - methyl - 3 - phenoxy - 2-butanol; 4 - benzyl - 2 - (1 - methyl - 1-phenoxyethyl)morpholine - 5 - one; and 4-benzyl - 2 - (1 - methyl - 1 - phenoxyethyl)-morpholine (hydrochloride m.p. 216—219° C.).

The 1 - benzylamino - 3 - methyl - 3-phenoxy-2-butanol is isolated by dissolving the cooled reaction mixture in 50 ml. of ether and adding an excess of a saturated ethereal hydrogen chloride solution. The mixture is filtered, the precipitated benzylamine hydrochloride being discarded, and the ethereal filtrate is washed five times with 50 ml. of aqueous 2N-sodium hydroxide solution each time, then washed once with water, dried and evaporated to dryness. The residue consists of 1-benzylamino-3-methyl-3-phenoxy-2-butanol.

Example 3

A solution of 6 g. of 4-benzyl-2-(1-phenoxy)morpholine hydrogen oxalate in 100 ml. of absolute ethanol is shaken with 1 g. of a 5% palladium-on-charcoal catalyst in an atmosphere of hydrogen at room temperature and at a pressure of one atmosphere until

uptake of hydrogen ceases. The mixture is filtered and the solvent is removed by evaporation under reduced pressure. The residue is crystallised from a mixture of methylated spirits and ether and there is thus obtained 2-(1-phenoxyethyl)morpholine hydrogen oxalate, m.p. 94—96° C.

The 4-benzyl-2-(1-phenoxyethyl)morpholine hydrogen oxalate used as starting material may be obtained by a similar process to that described in the second part of Example 1, except that 18 g. of the known compound 1,2-epoxy-3-phenoxybutane (Journal of Organic Chemistry, 1960, *25*, 863) are used instead of the 1,2-epoxy-2-methyl-3-phenoxypropane, and that equivalent amounts of the other reagents and solvents are used. There are thus obtained successively 1-benzylamino-3-phenoxy-2-butanol (isolated by the procedure described in Example 2 for the isolation of 1 - benzylamino - 3 - methyl - 3-phenoxy - 2 - butanol); 1 - (*N* - benzylchloroacetamido) - 3 - phenoxy - 2 - butanol; 4 - benzyl - 2 - (1 - phenoxyethyl)morpholine-5 - one; and 4 - benzyl - 2 - (1 - phenoxyethyl)morpholine hydrogen oxalate (m.p. 157—160° C. after crystallisation from a mixture of ethanol and ether).

Example 4

The process described in the last paragraph of Example 1 is repeated except that an equivalent amount of 2 - (*o* - ethoxyphenoxymethyl) - 4 - isopropyl - 2 - methylmorpholine-5-one is used as starting material in place of the 4-benzyl-2-methyl-2-phenoxymethylmorpholine-5-one. There is thus obtained 2 - (*o* - ethoxyphenoxymethyl)-4 - isopropyl - 2 - methylmorpholine.

The 2 - (*o* - ethoxyphenoxymethyl) - 4-isopropyl - 2 - methylmorpholine - 5 - one used as starting material may be obtained as follows:—

A solution of 25 g. of chloroacetone and 1.5 g. of potassium iodide in 25 ml. of dry acetone is added during 30 minutes to a vigorously stirred mixture of 27.6 g. of *o*-ethoxyphenol, 28.5 g. of anhydrous potassium carbonate and 75 ml. of dry acetone which is heated under reflux. Stirring and heating is continued for a further 8 hours, the mixture is allowed to cool at ambient temperature and stirring is continued for a further 20 hours. The mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is dissolved in 100 ml. of chloroform and the chloroform solution is washed twice with 30 ml. of 2N sodium hydroxide solution and once with 50 ml. of water, and is then dried over anhydrous magnesium sulphate. The chloroform is removed by evaporation under reduced pressure and the residue is crystallised from cyclohexane. There is thus obtained *o*-ethoxyphenoxyacetone, m.p. 42° C.

The process described in the second part of Example 1 is repeated except that an equivalent amount of *o*-ethoxyphenoxyacetone is used in place of the phenoxyacetone. There is thus obtained 1,2-epoxy-3-*o*-ethoxyphenoxy-2-methylpropane. A solution of 20 g. of this compound in 200 ml. of ethanol and 35 ml. of isopropylamine is heated under reflux for 18 hours. The ethanol and excess of isopropylamine are removed by evaporation under reduced pressure, the residue is dissolved in 100 ml. of ether and the ethereal solution is extracted 4 times with 50 ml. of aqueous 2N-hydrochloric acid each time. The combined acidic extracts are basified with aqueous 11N-sodium hydroxide solution and extracted three times with ether. The combined ethereal extracts are washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. There is thus obtained 1-*o*-ethoxyphenoxy-3-isopropylamino - 2 - methyl - 2 - propanol (characterised as the hydrogen oxalate, m.p. 104—105° C. after crystallisation from a mixture of methanol and ether).

The process described in the third part of Example 1 is repeated using an equivalent amount of this compound in place of 1-benzylamino - 2 - methyl - 3 - phenoxy - 2-propanol. There are thus obtained successively 1 - *o* - ethoxyphenoxy - 3 - (*N* - isopropylchloroacetamido) - 2 - methyl - 2 - propanol and 2 - (*o* - ethoxyphenoxymethyl) - 4 - isopropyl - 2 - methylmorpholine - 5 - one, which are both used without further purification.

Example 5

The process described in the last paragraph of Example 1 is repeated except that an equivalent amount of 2 - (*o* - ethoxyphenoxymethyl) - 2 - ethyl - 4 - isopropylmorpholin-5-one is used as starting material in place of the 4 - benzyl - 2 - methyl - 2 - phenoxymethylmorpholine - 5 - one. There is thus obtained 2 - (*o* - ethoxyphenoxymethyl) - 2-ethyl - 4 - isopropylmorpholine, characterised as the picrate thereof, m.p. 79—82° C. after crystallisation from aqueous methanol.

The 2 - (*o* - ethoxyphenoxymethyl) - 2-ethyl - 4 - isopropylmorpholine - 5 - one used as starting material may be obtained as follows:—

A mixture of 27.6 g. of *o*-ethoxyphenol, 15.1 g. of chloroacetonitrile, 27.6 g. of anhydrous potassium carbonate and 200 ml. of dry acetone is vigorously stirred and heated under reflux for 18 hours. The mixture is cooled and filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is dissolved in 100 ml. of ether and the ethereal solution is washed twice with 25

ml. of aqueous 2N-sodium hydroxide solution and then with 50 ml. of water, and is then dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. The residue is crystallised at 0° C. from petroleum ether (b.p. 30—40° C.) and there is thus obtained *o*-ethoxyphenoxy-acetonitrile, m.p. 38—45° C. A solution of 8.85 g. of this compound in 50 ml. of dry ether is added dropwise to a well-stirred solution of ethyl magnesium iodide prepared by conventional means from 11.7 g. of ethyl iodide and 1.8 g. of magnesium in 80 ml. of dry ether. After completion of the addition, the mixture is stirred and heated under reflux for one hour and then cooled to 0° C., and 50 ml. of ice-cold aqueous N-hydrochloric acid solution are added dropwise. The ethereal layer is separated, washed with 50 ml. of water, dried and evaporated to dryness under reduced pressure. The residue is distilled and there is thus obtained 1-*o*-ethoxyphenoxybutan-2-one, b.p. 138—142° C./2 mm.

The process described in the third and fourth parts of Example 4 is repeated except that an equivalent amount of 1-*o*-ethoxyphenoxybutan-2-one is used in place of the *o*-ethoxyphenoxyacetone. There are thus obtained successively 1,2 - epoxy - 3 - *o* - ethoxyphenoxy - 2 - ethylpropane, 1 - *o* - ethoxyphenoxy - 2 - ethyl - 3 - isopropylamino-2-propanol (characterised as the hydrogen oxalate thereof, m.p. 128—130° C. after crystallisation from ethylacetate containing 1% by volume of methanol); 1-*o*-ethoxyphenoxy-2 - ethyl - 3 - (*N* - isopropylchloroacetamido)-2 - propanol and 2 - (*o* - ethoxyphenoxymethyl) - 2 - ethyl - 4 - isopropylmorpholine-5-one.

Example 6

The process described in the last paragraph of Example 1 is repeated except that an equivalent amount of 2 - (*o* - ethoxyphenoxymethyl) - 4 - isopropyl - 2 - n-propylmorpholine-5-one is used as starting material in place of the 4-benzyl-2-methyl-2 - phenoxymethylmorpholine - 5 - one. There is thus obtained 2 - (*o* - ethoxyphenoxymethyl) - 4 - isopropyl - 2 - n-propylmorpholine as an oil.

The 2 - (*o* - ethoxyphenoxymethyl) - 4-isopropyl - 2 - n - propylmorpholine - 5 - one used as starting material may be obtained from *o*-ethoxyphenol by a similar sequence of steps to those set out in the second and third parts of Example 5, except that n-propyl magnesium iodide is used in place of ethyl magnesium iodide. The intermediates which are characterised are 1-*o*-ethoxyphenoxypentan-2-one (b.p. 152—156° C./2 mm.) and 1 - *o* - ethoxyphenoxy - 3-isopropylamino - 2 - n - propyl - 2 - propanol (hydrogen oxalate, m.p. 128—130° C. after crystallisation from ethyl acetate).

Example 7

The process described in the last paragraph of Example 1 is repeated except that an equivalent amount of either 2 - (*o* - chlorophenoxymethyl) - 4 - isopropyl- or 4 - allyl-2-methylmorpholine-5-one is used as starting material in the place of the 4-benzyl-2-methyl - 2 - phenoxymethylmorpholine - 5-one. There is thus obtained, respectively, 2-(*o* - chlorophenoxymethyl) - 4 - isopropyl-2 - methylmorpholine or 4 - allyl - 2 - (*o*-chlorophenoxymethyl) - 2 - methylmorpholine (oxalate hemihydrate, m.p. 107—109° C. after crystallisation from ethyl acetate).

The 2 - (*o* - chlorophenoxymethyl) -4-isopropyl- and 4 - allyl - 2 - methylmorpholin-5-ones used as starting materials may be obtained by similar processes to those described in the second, third and fourth parts of Example 4 except that *o*-chlorophenol is used in place of *o*-ethoxyphenol. The intermediates which are characterised are *o*-chlorophenoxyacetone (b.p. 105—114° C./2.5—3 mm.); 1 - *o* - chlorophenoxy - 3-isopropylamino - 2 - methyl - 2 - propanol (hydrogen oxalate, m.p. 145—147° C. after crystallisation from a mixture of methanol and ether); and 1 - allylamino - 3 - *o*-chlorophenoxy - 2 - methyl - 2 - propanol (hydrogen oxalate, m.p. 146—148° C. after crystallisation from a mixture of methanol and ether).

Example 8

The process described in the last paragraph of Example 1 is repeated except that an equivalent amount of either 2-(1-*o*-ethoxyphenoxy - 1 - methylethyl)- or 2 - (1 - *o*-tolyloxy - 1 - methylethyl) - 4 - isopropyl-2 - methylmorpholine - 5 - one is used as starting material in place of the 4-benzyl-2-methyl - 2 - phenoxymethylmorpholine - 5-one. There is thus obtained, respectively, 2-(1 - *o* - ethoxyphenoxy - 1 - methylethyl)-4 - isopropyl - 2 - methylmorpholine (hydrogen oxalate, m.p. 145—147° C. after crystallisation from a mixture of methanol and ether) and 2 - (1 - *o* - tolyloxy - 1 - methylethyl) - 4 - isopropyl - 2 - methylmorpholine (hydrogen oxalate, m.p. 112—114° C. after crystalisation from a mixture of ethyl acetate and ether).

The 2 - (1 - *o* - ethoxyphenoxy - 1-methylethyl - 4 - isopropyl - 2 - methylmorpholin-5-one used as starting material may be obtained as follows:—

A solution of 29.25 g. of 3-bromo-3-methyl-2-butanone in 25 ml. of dry acetone is added dropwise during 15 minutes to a vigorously stirred mixture of 25 g. of *o*-ethoxyphenol, 28 g. of anhydrous potassium carbonate and 75 ml. of dry acetone which is heated under reflux, and the mixture is stirred and heated under reflux for a further 8 hours. The mixture is cooled to ambient temperature and

stirring is continued for a further 20 hours. The mixture is filtered and the residue is washed with dry acetone. The combined filtrate and washings are evaporated to dryness under reduced pressure, and the residue is dissolved in 100 ml. of chloroform. The chloroform solution is washed twice with 50 ml. of aqueous 2N-sodium hydroxide solution and then with 50 ml. of water, dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. The residue is distilled and there is thus obtained 3 - *o* - ethoxyphenoxy - 3 - methylbutan-2-one, b.p. 90—102° C./0.7—1 mm.

The process described in the third and fourth parts of Example 4 is repeated except that an equivalent amount of 3-*o*-ethoxyphenoxy-3-methylbutan-2-one is used in place of the *o*-ethoxyphenoxyacetone. There are thus obtained successively 1,2 - epoxy-2,3 - dimethyl - 3 - (*o* - ethoxyphenoxy)-butane; 3 - (*o* - ethoxyphenoxy) - 1 - isopropylamino - 2,3 - dimethyl - 2 - butanol (characterised as the oxalate thereof, m.p. 174—175° C., after crystallisation from a mixture of methanol and ether); 3-(o-ethoxyphenoxy) - 1 - (N - isopropylchloroacetamido)-2,3 - dimethyl - 2 - butanol; and 2 - (1 - *o*-ethoxyphenoxy - 1 - methylethyl) - 4 - isopropyl - 2 - methylmorpholin - 5 - one.

The 2 - (1 - *o* - tolyloxy - 1 - methylethyl) - 4 - isopropyl - 2 - methylmorpholin-5-one used as starting material may be obtained by a similar process to that described above, except that *o*-cresol is used in place of *o*-ethoxyphenol. The intermediates which are characterised are 3 - methyl - 3 - *o*-tolyloxybutan - 2 - one (b.p. 75—80° C./0.7—1.0 mm.) and 1 - isopropylamino - 2,3-dimethyl - 3 - *o* - tolyloxy - 2 - butanol (hydrogen oxalate, m.p. 130—132° C. after crystallisation from a mixture of methanol and ether).

Example 9

The process described in the last paragraph of Example 1 is repeated except that an equivalent amount of 2 - (1 - *o* - ethoxyphenoxyethyl) - 4 - isopropyl - 2 - methylmorpholine-5-one is used as starting material in place of the 4 - benzyl - 2 - methyl-2 - phenoxymethylmorpholine - 5 - one. There is thus obtained 2 - (1 - *o* - ethoxyphenoxyethyl) - 4 - isopropyl - 2 - methylmorpholine as an oil.

The 2 - (1 - *o* - ethoxyphenoxyethyl)-4 - isopropyl - 2 - methylmorpholine - 5 - one used as starting material may be obtained by a similar process to that described in the second and third parts of Example 8 except that 3-bromo-2-butanone is used in place of 3 - bromo - 3 - methyl - 2 - butanone. The intermediates which are characterised are 3-*o* - ethoxyphenoxybutan - 2 - one (b.p. 95—106° C./0.9—1.3 mm.) and 3 - *o*-ethoxyphenoxy - 1 - isopropylamino - 2-methyl-2-butanol (hydrogen oxalate, m.p. 93—95° C. after crystallisation from a mixture of ethyl acetate and ether).

Example 10

The process described in the last paragraph of Example 1 is repeated except that an equivalent amount of 2 - (1 - *o*-ethoxyphenoxy - 1 - methylethyl)- or 2 - (1-*m* - methoxyphenoxy - 1 - methylethyl) - 4-isopropylmorpholin-5-one is used as starting material in place of the 4-benzyl-2-methyl-2 - phenoxymethylmorpholin - 5 - one. There is thus obtained, respectively, 2 - (1 - *o*-ethoxyphenoxy - 1 - methylethyl) - 4 - isopropylmorpholine and 4 - isopropyl - 2-(1 - *m* - methoxyphenoxy - 1 - methylethyl)-morpholine, both as oils.

The 2 - (1 - *o* - ethoxyphenoxy - 1-methylethyl) - 4 - isopropylmorpholin - 5-one used as starting material may be obtained as follows:—

A vigorously stirred mixture of 21.4 g. of *o*-ethoxyphenol, 127 ml. of acetone and 36 g. of sodium hydroxide pellets is heated to boiling under reflux and 16 ml. of chloroform are then added dropwise at such a rate that the mixture continues to boil without further application of heat. When addition is completed the mixture is stirred and heated under reflux for a further 5 hours. The acetone is removed by distillation under reduced pressure and the residue is dissolved in 500 ml. of aqueous 2N-hydrochloric acid. The acidic solution is extracted three times with 200 ml. of chloroform each time and the combined extracts are stirred while 500 ml. of saturated aqueous sodium bicarbonate solution are added. Stirring is continued for one hour, the aqueous layer is separated and the chloroform layer is extracted twice with 200 ml. of sodium bicarbonate solution each time. The combined bicarbonate extracts are carefully acidified with aqueous 2N-hydrochloric acid and the mixture is filtered. The residue is dried and crystallised from cyclohexane and there is thus obtained 2-(*o*-ethoxyphenoxy)-2-methylpropionic acid, m.p. 64° C.

A solution of 18 g. of this product in 100 ml. of dry ether is added dropwise to a stirred suspension of 5 g. of lithium aluminium hydride in 200 ml. of dry ether at such a rate that the mixture boils gently, and the mixture is then stirred and heated under reflux for 18 hours. The mixture is cooled and the excess of lithium aluminium hydride is decomposed by successive addition of 5 ml. of water, 5 ml. of aqueous 2N-sodium hydroxide solution and 15 ml. of water. The mixture is filtered, the ether is removed from the filtrate by distillation under reduced pressure and the residue is distilled. There is thus obtained 2 - *o* - ethoxyphenoxy - 2-methyl-1-propanol, b.p. 117° C./3 mm.

A mixture of 14 g. of this compound, 57 g. of dicyclohexyl-carbodiimide and 270 ml. of dry dimethylsulphoxide is stirred and heated at 90—95° C. for one hour when complete solution has taken place. 2.7 Ml. of 85% aqueous phosphoric acid are added and the mixture is stirred and heated at 90—95° C. for one hour. The mixture is cooled to ambient temperature and stirring is continued for 16 hours. The mixture is then heated at 90—95° C. and stirring is continued for one further hour. 18 Ml. of water are added and the mixture is cooled to ambient temperature. The mixture is filtered and the residue is washed with 500 ml. of water and then with 500 ml. of ether. The combined filtrate and washings are shaken together and the layers are separated. The aqueous layer is extracted twice with 200 ml. of ether each time and the combined ethereal solutions are washed three times with 200 ml. of water each time, dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. The residue is distilled and there is thus obtained 2-*o*-ethoxyphenoxy - 2 - methylpropionaldehyde, b.p. 108—110° C./3.5 mm.

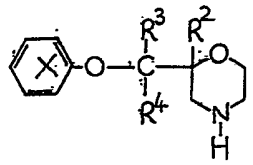
The process described in the third and fourth parts of Example 4 is repeated except that an equivalent amount of 2-*o*-ethoxyphenoxy - 2 - methylpropionaldehyde is used in place of the *o*-ethoxyphenoxyacetone. There are thus obtained successively 1,2-epoxy - 3 - (*o* - ethoxyphenoxy) - 3 - methylbutane; 3 - (*o* - ethoxyphenoxy) - 1 - isopropylamino - 3 - methyl - 2 - butanol (characterised as the hydrogen oxalate, m.p. 134—136° C. after crystallisation from a mixture of methanol and ether); 3 - (*o* - ethoxyphenoxy) - 1 - (*N* - isopropylchloroacetamido) - 3 - methyl - 2 - butanol; and 2-(1 - *o* - ethoxyphenoxy - 1 - methylethyl) - 4-isopropylmorpholin - 5 - one.

The 2 - (1 - *m* - methoxyphenoxy - 1-methylethyl) - 4 - isopropylmorpholin - 5-one used as starting material may be obtained by a similar process to that described above, except that *m*-methoxyphenol is used in place of *o*-ethoxphenol. The intermediates which are characterised are 2-*m*-methoxyphenoxy - 2 - methyl - 1 - propanol (b.p. 110—112° C./1.2 mm.); 2 - *m* - methoxyphenoxy - 2 - methylpropionaldehyde (b.p. 108—112° C./3.5 mm.) and 1-isopropylamino - 3 - *m* - methoxyphenoxy - 3-methyl-2-butanol (hydrogen oxalate, m.p. 100—102° C. after crystallisation from a mixture of methanol and ether).

Example 11

Phenyl chloroformate (1.6 g.) is added to a solution of 2.9 g. of 2-*o*-ethoxyphenoxymethyl - 4 - isopropyl - 2 - methylmorpholine (Example 4) in 50 ml. of dry benzene and the mixture is heated under reflux for 18 hours. The solvent is removed by evaporation under reduced pressure and the residue is dissolved in a solution of 6 g. of potassium hydroxide in 60 ml. of *n*-propanol. The mixture is heated under reflux for 48 hours, the solvent is removed by evaporation under reduced pressure and the residue is dissolved in 100 ml. of aqueous 2N-hydrochloric acid. The acidic solution is washed twice with 30 ml. of ether each time and is then basified with aqueous 11N-sodium hydroxide solution and extracted three times with 50 ml. of ether each time. The combined ethereal extracts are washed with water, dried over anhydrous magnesium sulphate and filtered. The ether is removed by evaporation under reduced pressure and the residual free base is converted to the oxalate salt thereof by conventional means. The oxalate is crystallised from a mixture of ethanol and ether and there is thus obtained 2 - (*o* - ethoxyphenoxymethyl) - 2 - methylmorpholine hydrogen oxalate hemihydrate, m.p. 68—70° C. (with decomposition).

The process described above is repeated except that the appropriate 4-isopropylmorpholine derivative, prepared as described in the foregoing Examples 5 to 10, is used in place of 2 - *o* - ethoxyphenoxymethyl - 4-isopropyl - 2 - methylmorpholine. There are thus obtained the compounds shown in the following table:—



Substituent in ring X	R^2	R^3	R^4	m.p. (°C.) of salt	crystallisation solvent
o-ethoxy	ethyl	H	H	hydrogen oxalate monohydrate 57—59(d)	ethyl acetate
o-ethoxy	n-propyl	H	H	hydrogen oxalate hemihydrate 54—56(d)	ethyl acetate/ ether
o-chloro	methyl	H	H	oxalate hemihydrate 130—132	methanol/ether
o-ethoxy	methyl	methyl	methyl	hydrogen oxalate 120—122	methanol/ether
o-methyl	methyl	methyl	methyl	oxalate 170—172	methanol/ether
o-ethoxy	methyl	methyl	H	hydrogen oxalate 132—134	methanol/ether
o-ethoxy	H	methyl	methyl	hydrogen oxalate 131—133	methanol/ether
m-methoxy	H	methyl	methyl	oxalate 192—193	methanol/ether

Example 12

A solution of 2.5 g. of 4 - benzyl-2 - (*m* - methoxyphenoxymethyl) - 2 - methylmorpholine hydrogen oxalate in a mixture of 100 ml. of ethanol and 10 ml. of water is shaken with 1 g. of a 5% palladium-on-charcoal catalyst in an atmosphere of hydrogen at room temperature and at a pressure of one atmosphere until uptake of hydrogen ceases. The mixture is filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is crystallised from a mixture of methanol and ether and there is thus obtained 2-(*m*-methoxyphenoxymethyl)-2-methylmorpholine hydrogen oxalate, m.p. 140—141° C.

The 4 - benzyl - 2 - (*m* - methoxyphenoxymethyl) - 2 - methylmorpholine used as starting material may be obtained by a similar process to that described in the second, third and fourth parts of Example 1, except that an equivalent amount of *m*-methoxyphenoxyacetone is used in place of phenoxyacetone. There are thus obtained successively 1,2 - epoxy - 3 - (*m* - methoxyphenoxy) - 2 - methylpropane; 1 - benzylamino - 3 - (*m* - methoxyphenoxy) - 2-methyl-2-propanol (characterised as the hydrogen oxalate, m.p. 179—180° C. after crystallisation from a mixture of methanol and ether); 1 -(*N* - benzylchloroacetamido)-3 - (*m* - methoxyphenoxy) - 2 - methyl - 2-

propanol; 4 - benzyl - 2 - (*m* - methoxyphenoxymethyl) - 2 - methylmorpholin - 5-one; and 4 - benzyl - 2 - (*m* - methoxyphenoxymethyl)-2-methylmorpholine (hydrogen oxalate, m.p. 167—168° C. after crystallisation from methanol).

The *m*-methoxyphenoxyacetone (b.p. 118° C./1.5 mm.) may itself be obtained by a similar process to that described in the second part of Example 4 for the preparation of *o*-ethoxyphenoxyacetone, except that an equivalent amount of *m*-methoxyphenol is used in place of *o*-ethoxyphenol.

Example 13

A solution of 1.6 g. of 4-benzyl-2-(*m*-methoxyphenoxymethyl-2-methyl morpholine and 0.7 g. of phenyl chloroformate in 30 ml. of dry benzene is heated under reflux for 24 hours and then evaporated to dryness under reduced pressure. The residue is dissolved in a solution of 3 g. of potassium hydroxide in 20 ml. of ethanol and the mixture is heated under reflux for 24 hours and then evaporated to dryness under reduced pressure. The residue is dissolved in 50 ml. of aqueous 2N-hydrochloric acid and the acidic solution is washed twice with 20 ml. of ethyl acetate each time and is then basified with aqueous 11N-sodium hydroxide solution. The mixture is extracted four times with 30 ml. of ethyl acetate each time and the combined ethyl acetate extracts are washed with 50 ml. of water, dried and evaporated to dryness under reduced pressure. The residual free base is converted into the oxalate thereof by conventional means and there is thus obtained 2-(*m* - methoxyphenoxymethyl) - 2 - methylmorpholine hydrogen oxalate, m.p. 140—141° C. after crystallisation from a mixture of methanol and ether.

Example 14

A solution of 5.3 g. of *cis* - 2 - *o*-ethoxyphenoxy - 4' - isopropylcyclohexane-spiro - 2' - morpholine - 5' - one in 50 ml. of dry tetrahydrofuran is added dropwise to a stirred suspension of 1 g. of lithium aluminium hydride in 150 ml. of dry ether and the mixture is stirred and heated under reflux for 18 hours. The mixture is cooled and the excess of lithium aluminium hydride is decomposed by the successive addition, with stirring, of 1 ml. of water, 1 ml. of aqueous 2N-sodium hydroxide solution and 3 ml. of water. The mixture is stirred for 30 minutes and filtered and the filtrate is evaporated to dryness under reduced pressure. There is thus obtained as residue *cis* - 2 - *o*-ethoxyphenoxy - 4' - isopropylcyclohexane-spiro-2'-morpholine, which is characterised by conversion by conventional means to the hydrogen oxalate salt thereof, m.p. 146—147° C. after crystallisation from a 1% v/v solution of methanol in ethyl acetate.

The *cis* - 2 - *o* - ethoxyphenoxy - 4'-isopropylcyclohexane - spiro - 2' - morpholin-5'-one used as starting material may be obtained as follows:—

13.25 G. of 2-chlorocyclohexanone are added to a stirred mixture of 13.8 g. of *o*-ethoxyphenol, 13.8 g. of anhydrous potassium carbonate and 100 ml. of dry acetone and the mixture is stirred and heated under reflux for 18 hours. The mixture is cooled and filtered and the filtrate is evaporated to dryness under reduced pressure. The residue is dissolved in 100 ml. of ethyl acetate and the ethyl acetate solution is washed successively with aqueous 2N-sodium hydroxide solution and water and then dried. The solvent is removed by evaporation under reduced pressure and the residue is distilled. There is thus obtained 2-*o*-ethoxyphenoxycyclohexanone, b.p. 84—86° C./13—14 mm.

2.3 G. of a 50% dispersion of sodium hydride in mineral oil are added to a stirred suspension of 10.56 g. of trimethylsulphoxonium iodide in 60 ml. of dry dimethylsulphoxide and the mixture is stirred and heated at 50—60° C. in an atmosphere of nitrogen until evolution of hydrogen ceases and a clear solution is formed. A solution of 9.36 g. of 2-*o*-ethoxyphenoxycyclohexanone in 10 ml. of dry dimethylsulphoxide is added and the mixture is stirred and heated at 50—60° C. in an atmosphere of nitrogen for a further 4 hours. The mixture is cooled, diluted with 200 ml. of water and extracted with ethyl acetate (3×60 ml.). The combined ethyl acetate extracts are washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness under reduced pressure. The residue is dissolved in a 1:1 v/v mixture of benzene and petroleum ether (b.p. 60—80° C.) and the solution is added to a 200 g. chromatography column of silica gel ("Florisil"; "Florisil" is a Registered Trade Mark). The column is eluted with 300 ml. of the 1:1 v/v mixture of benzene and petroleum ether (b.p. 60—80° C.) to remove the mineral oil, and elution is continued with benzene alone, fractions of 150 ml. being collected. The first eight fractions are combined and evaporated to dryness under reduced pressure and there is thus obtained as residue *cis* - 2 - *o* - ethoxyphenoxycyclohexanespirooxiran. The following six fractions are discarded and elution is then continued with a 9:1 v/v mixture of benzene and ethyl acetate. The next ten fractions are combined and evaporated under reduced pressure and there is thus obtained *trans*-2-*o*-ethoxyphenoxycyclohexanespirooxiran.

A solution of 2.7 g. of *cis*-2-*o*-ethoxyphenoxycyclohexanespirooxiran in a mixture of 60 ml. of ethanol and 15 ml. of isopropylamine is heated under reflux for 5 hours. The mixture is evaporated to dryness under reduced pressure, the residue is dissolved in aqueous

2N-hydrochloric acid and the solution is extracted with ether (2×50 ml.), the extracts being discarded. The acidic solution is basified with aqueous 11N-sodium hydroxide solution and extracted with ether (3×50 ml.). The combined ethereal extracts are washed with water and dried and the ether is removed by evaporation under reduced pressure. There is thus obtained *cis* - 2 - *o*-ethoxyphenoxy - 1 - isopropylaminomethylcyclohexan-1-ol, characterised as the normal oxalate thereof, m.p. 162—164° C. after crystallisation from isopropanol.

1.74 Ml. of chloroacetyl chloride are added dropwise to a stirred solution of 7.0 g. of *cis*-1 - isopropylaminomethyl - 2 - *o* - ethoxyphenoxycyclohexan-1-ol and 3.22 ml. of triethylamine in 50 ml. of dry methylene chloride which is kept at 0° C., and the mixture is stirred at ambient temperature for 18 hours. The mixture is washed successively with aqueous 2N-hydrochloric acid and water, dried and the solvent is removed by evaporation under reduced pressure. There is thus obtained *cis* - 2 - *o* - ethoxyphenoxy - 1-*N* - isopropylchloroacetamidocyclohexan - 1 - ol. This compound is added to a solution of 0.54 g. of sodium in 120 ml. of dry methanol and the mixture is heated under reflux for 18 hours. The methanol is removed by evaporation under reduced pressure, the residue is dissolved in 100 ml. of ether and the ethereal solution is washed successively with aqueous 2N-hydrochloric acid and water, and then dried. The ether is removed by evaporation under reduced pressure and there is thus obtained as residue *cis*-2-*o*-ethoxyphenoxy - 4' - isopropylcyclohexanespiro - 2'-morpholine-5'-one.

It is to be understood that in this specification the expression *cis*- applied to a cyclohexane derivative indicates that the two oxygen atoms attached to the cyclohexane ring, for example one oxygen atom of an aryloxy radical such as the *o*-ethoxyphenoxy radical, and a second oxygen atom of an oxiran ring, or of a hydroxy radical, or of a morpholine ring, are one in an equatorial conformation and one in an axial conformation with respect to the cyclohexane ring. It is further to be understood that the expression *trans*- applied to a cyclohexane derivative indicates that the two oxygen atoms such as are described above are either both in equatorial conformations, or both in axial conformations, with respect to the cyclohexane ring.

Example 15

The process described in Example 14 is repeated except that 5.6 g. of *trans*-2-*o*-ethoxyphenoxy - 4' - isopropylcyclohexanespiro - 2' - morpholin - 5' - one are used in place of the corresponding *cis*-isomer. There is thus obtained *trans* - 2 - *o* - ethoxyphenoxy - 4' - isopropylcyclohexanespiro - 2'-morpholine, which is characterised by conversion by conventional means to the hydrogen oxalate monohydrate thereof, m.p. 131—133° C.

The *trans* - 2 - *o* - ethoxyphenoxy - 4'-isopropylcyclohexanespiro - 2' - morpholin-5'-one used as starting material may be obtained by a similar process to that described in the two penultimate paragraphs of Example 14, except that *trans*-2-*o*-ethoxyphenoxycyclohexanespirooxiran is used as starting material in place of the *cis*-isomer. There are thus obtained successively *trans*-2-*o*-ethoxyphenoxy - 1 - isopropylaminomethylcyclohexan-1-ol (characterised as the hydrogen oxalate, m.p. 150—152° C. after crystallisation from isopropanol); *trans* - 2 - *o* - ethoxyphenoxy 1 - *N* - isopropylchloroacetamidomethylcyclohexan - 1 - ol; and *trans* - 2-*o* - ethoxyphenoxy - 4' - isopropylcyclohexane - spiro - 2' - morpholin - 5' - one.

The *trans* - 2 - *o* - ethoxyphenoxycyclohexanespirooxiran may itself be obtained as described in Example 14. Alternatively, it may be obtained by the following process which confirms its identity as the *trans*-isomer:—

0.5 G. of a 50% dispersion of sodium hydride in mineral oil is added to 8 ml. of dry dimethylsulphoxide and the mixture is stirred and heated at 70—75° C. in an atmosphere of nitrogen until evolution of hydrogen ceases. The mixture is cooled to ambient temperature and 10 ml. of dry tetrahydrofuran are added. The mixture is stirred and cooled to between −10 and −5° C. and a solution of 2.14 g. of trimethylsulphonium iodide in 20 ml. of dry dimethylsulphoxide is added during 3 minutes. The mixture is stirred for a further 2 minutes and a solution of 2.34 g. of 2-*o*-ethoxyphenoxycyclohexanone in 10 ml. of dry tetrahydrofuran is then added. The mixture is stirred for 15 minutes at between −10 and −5° C. and then for 1 hour at ambient temperature. The mixture is diluted with 100 ml. of water and extracted with ethyl acetate (3×50 ml.). The combined extracts are washed with water, dried and evaporated to dryness under reduced pressure. There is thus obtained as residue *trans* - 2 - *o* - ethoxyphenoxycyclohexanespirooxiran which is essentially uncontaminated with the isomeric *cis*-compound.

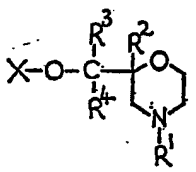
Example 16

The process described in Example 11 is repeated except that an equivalent amount of *cis*- or *trans* - 2 - *o* - ethoxyphenoxy - 4'-isopropylcyclohexanespiro - 2' - morpholine is used as starting material in place of the 2 - *o* - ethoxyphenoxymethyl - 4 - isopropyl-2-methylmorpholine. There are thus obtained, respectively, *cis* - 2 - *o* - ethoxyphenoxycyclohexanespiro - 2' - morpholine, characterised as the hydrogen oxalate hemihydrate

thereof, m.p. 126—128° C. (crystallised from a 1% v/v solution of methanol in ethyl acetate), and *trans* - 2 - *o* - ethoxyphenoxycyclohexanespiro - 2' - morpholine, characterised as the hydrogen oxalate sesquihydrate thereof, m.p. 158—160° C. (crystallised from a mixture of ethyl acetate and methanol).

WHAT WE CLAIM IS:—

1. Morpholine derivatives of the formula:—



wherein R^1 stands for hydrogen or for an alkyl, alkenyl or cycloalkyl radical, wherein R^2, R^3 and R^4, which may be the same or different, stand for hydrogen or for alkyl radicals, provided that R^2, R^3 and R^4 do not all stand for hydrogen, or wherein R^2 and R^3 are joined, together with the two adjacent carbon atoms, to form a cycloalkyl ring and R^4 stands for hydrogen or for an alkyl radical and wherein X stands for an aryl radical which may optionally be substituted, and the acid-addition salts thereof.

2. Morpholine derivatives as claimed in claim 1 wherein R^1 stands for hydrogen or for an alkyl or alkenyl radical each of up to 6 carbon atoms or for a cycloalkyl radical of up to 5 carbon atoms, wherein R^2, R^3 and R^4, which may be the same or different, stand for hydrogen or for alkyl radicals of up to 3 carbon atoms, provided that R^2, R^3 and R^4 do not all stand for hydrogen, or wherein R^2 and R^3 are joined, together with the two adjacent carbon atoms, to form a cycloalkyl ring of up to 8 carbon atoms and R^4 stands for hydrogen or for an alkyl radical of up to 3 carbon atoms, and wherein X stands for a phenyl or naphthyl radical which is unsubstituted or which is substituted by one or more substituents selected from halogen atoms, alkyl, alkoxy and alkylthio radicals each of up to 10 carbon atoms, halogenoalkyl and halogenoalkoxy radicals each of up to 5 carbon atoms, alkenyl, alkenyloxy, alkynyloxy and cycloalkoxy radicals each of up to 6 carbon atoms, aryl, aryloxy, alkylaryloxy, aralkyl and aralkoxy radicals each of up to 10 carbon atoms, alkyl radicals of up to 5 carbon atoms substituted by hydroxy radicals or by alkoxy radicals of up to 5 carbon atoms, alkanoyl radicals of up to 5 carbon atoms, alkanoylamino radicals of up to 6 carbon atoms, alkoxycarbonyl radicals of up to 6 carbon atoms, hydroxy, amino, carboxy, methylenedioxy and nitro radicals; and alkylene radicals of 3 or 4 carbon atoms, and the acid-addition salts thereof.

3. Morpholine derivatives as claimed in claim 1 wherein R^1 stands for hydrogen or for the methyl, ethyl, isopropyl, n-propyl, s-butyl, t-butyl, allyl, cyclopropyl, cyclobutyl or cyclopentyl radical, wherein R^2, R^3 and R^4, which may be the same or different, stand for hydrogen or for methyl, ethyl or n-propyl radicals, provided that R^2, R^3 and R^4 do not all stand for hydrogen, or wherein R^2 and R^3 are joined, together with the two adjacent carbon atoms, to form the cyclohexyl ring and R^4 stands for hydrogen or for the methyl, ethyl or n-propyl radical, and wherein X stands for a phenyl or naphthyl radical which is unsubstituted or which is substituted by one or two substituents selected from fluorine, chlorine, bromine and iodine atoms and methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, t-amyl, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, n-heptyloxy, methylthio, trifluoromethyl, 2,2-dichloro-1,1-difluoroethoxy, allyl, allyloxy, propargyloxy, cyclopentyloxy, phenyl, phenoxy, 4-tolyloxy, benzyl, benzyloxy, hydroxymethyl, 1-hydroxyethyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, n-propoxymethyl, methoxycarbonyl, ethoxycarbonyl, hydroxy, amino, carboxy, methylenedioxy, nitro, trimethylene and tetramethylene radicals, and the acid-addition salts thereof.

4. Morpholine derivatives of the formula given in claim 1 wherein R^1 stands for hydrogen or for an alkyl or alkenyl radical each of up to 6 carbon atoms or for a cycloalkyl radical of up to 5 carbon atoms, wherein R^2, R^3 and R^4, which may be the same or different, stand for hydrogen or for alkyl radicals of up to 3 carbon atoms, provided that R^2, R^3 and R^4 do not all stand for hydrogen, and wherein X has the meaning stated in claim 2, and the acid-addition salts thereof.

5. Morpholine derivatives as claimed in claim 4 wherein R^1 stands for hydrogen or for the methyl, ethyl, n-propyl, isopropyl, allyl or cyclopentyl radical, wherein R^2 stands for hydrogen or for the methyl, ethyl or n-propyl radical, wherein R^3 and R^4, which may be the same or different, stand for hydrogen or for methyl radicals, provided that R^2, R^3 and R^4 do not all stand for hydrogen, and wherein X has the meaning stated in claim 3, and the acid-addition salts thereof.

6. Morpholine derivatives as claimed in claim 5 wherein R^1 stands for hydrogen or for the isopropyl radical and wherein X stands for the phenyl, *o*-ethoxyphenyl or *m*-methoxyphenyl radical, and the acid-addition salts thereof.

7. Morpholine derivatives of the formula given in claim 1 wherein R^1 and X have the meanings stated in claim 6, wherein R^2 stands for the methyl, ethyl or n-propyl radical, and wherein R^3 and R^4 both stand for

hydrogen, and the acid-addition salts thereof.

8. Morpholine derivatives of the formula given in claim 1 wherein R^1 and X have the meanings stated in claim 6, and wherein either:—

a) R^2 and R^3 both stand for the methyl radical and R^4 stands for hydrogen; or

b) R^2, R^3 and R^4 all stand for the methyl radical; or

c) R^2 and R^3 both stand for hydrogen and R^4 stands for the methyl radical; or

d) R^2 stands for hydrogen and R^3 and R^4 both stand for the methyl radical;

and the acid-addition salts thereof.

9. Morpholine derivatives of the formula given in claim 1 wherein R^1 and X have the meanings stated in claim 6, wherein R^2 and R^3 are joined, together with the two adjacent carbon atoms, to form the cyclohexyl ring, and wherein R^4 stands for hydrogen, and the acid-addition salts thereof.

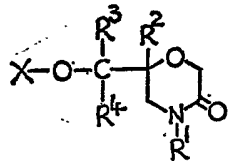
10. The compounds 2 - (1 - methyl - 1-phenoxyethyl)morpholine; 2 - (1 - phenoxyethyl)morpholine and 2 - methyl - 2-phenoxymethylmorpholine and the acid-addition salts thereof.

11. The compounds 2 - (1 - *o* - ethoxyphenoxy - 1 - methylethyl)morpholine and 2 - (1 - *o* - ethoxyphenoxy - 1 - methylethyl)-4-isopropylmorpholine and the acid-addition salts thereof.

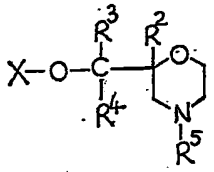
12. Acid-addition salts as claimed in any of claims 1 to 11 which are hydrochlorides, hydrobromides, phosphates, sulphates, oxalates, lactates, tartrates, acetates, gluconates, salicylates, citrates, ascorbates, benzoates, β-naphthoates, adipates or 1,1-methylene-bis-(2 - hydroxy - 3 - naphthoates) or acid-addition salts derived from sulphonated polystyrene resins.

13. Acid-addition salts as claimed in any of claims 4 to 8 and 10 which are hydrochlorides, hydrobromides, phosphates, sulphates, oxalates, lactates, tartrates, acetates, gluconates, salicylates, citrates, ascorbates, benzoates, β-naphthoates, adipates or 1,1-methylene - bis - (2 - hydroxy - 3 - naphthoates) or acid-addition salts derived from sulphonated polystyrene resins.

14. A process for the manufacture of morpholine derivatives and acid-addition salts thereof, claimed in any of claims 1 to 13, which comprises the reduction of a compound of the formula:—



wherein R^1, R^2, R^3, R^4 and X have the meanings stated in any of claims 1 to 9 with a complex metal hydride, or, for the manufacture of those of the morpholine derivatives wherein R^1 stands for hydrogen, which comprises the removal of the removable α-aryl-alkyl or alkyl radical from a compound of the formula:—



wherein R^2, R^3, R^4 and X have the meanings stated in any of claims 1 to 9 and wherein R^5 stands for a removable α-aryl-alkyl or alkyl radical, whereafter if an acid-addition salt is required, the morpholine derivative in free base form is reacted with an acid.

15. A process as claimed in claim 14 wherein the complex metal hydride is lithium aluminium hydride.

16. A process as claimed in claim 14 or 15 which is carried out in ether, tetrahydrofuran or 1,2-dimethoxyethane as diluent or solvent.

17. A process as claimed in claim 14 wherein R^5 stands for the benzyl radical.

18. A process as claimed in claim 14 or 17 wherein the α-aryl-alkyl radical is removed by catalytic hydrogenolysis in a diluent or solvent in the presence of a palladium-on-charcoal catalyst.

19. A process as claimed in claim 14 wherein R^5 stands for the methyl or isopropyl radical.

20. A process as claimed in claim 14, 17 or 19 wherein the α-aryl-alkyl or alkyl radical is removed by the interaction of the starting material with an alkyl or aryl chloroformate, followed by the hydrolysis of the alkoxy- or aryloxy-carbonyl derivative thus obtained.

21. A process as claimed in claim 20 wherein the chloroformate is methyl, ethyl or phenyl chloroformate.

22. Pharmaceutical compositions which comprise as active ingredient at least one of the morpholine derivatives or an acid-addition salt thereof, claimed in any of claims 1 to 13, in association with a pharmaceutically-acceptable diluent or carrier therefore.

23. Pharmaceutical compositions as claimed in claim 22 which are in the form of tablets, capsules, aqueous or oily solutions or suspensions, emulsions, injectable aqueous or oily solutions or suspensions, or dispersible powders.

24. Pharmaceutical compositions as claimed in claim 22 or 23 which also contain, in addition to the morpholine derivative or salt

thereof, one or more known drugs selected from neuroleptic agents, other sedative drugs and tranquillizers, anticonvulsant drugs, β-adrenergic blocking agents, drugs used in the treatment of Parkinson's disease, and other antidepressant drugs.

25. Pharmaceutical compositions as claimed in claim 22, 23 or 24 which are suitable for oral administration in unit dosage form, as tablets and capsules which contain between 1 and 100 mg. of active ingredient.

26. Morpholine derivatives and acid-addition salts thereof, claimed in any of claims 4 to 8, 10 and 13, as hereinbefore particularly described in Examples 1 to 3.

27. Morpholine derivatives and acid-addition salts thereof, claimed in any of claims 1 to 13, as hereinbefore particularly described in Examples 1 to 16.

28. A process for the manufacture of morpholine derivatives and acid-addition salts thereof, claimed in any of claims 14 to 21, as hereinbefore particularly described in Examples 1 to 16.

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